wherein said peptides are of the form

$(Xaa)_m$-R1-$(Xaa)_n$,

where R1 is the amino acid at said first fixed position, and m and n do not differ by more than two,

in which R1 is tryptophan, proline or tyrosine.

34 (amended). The panel of claim 33 where the panel has an overall diversity which is the same at each position of the peptides, and a given library has a diversity at a biased position which does not exceed 3.

38 (amended). The panel of claim 27 wherein the overall diversity of the panel at the fixed position of the peptides is the same as the overall diversity of the panel at each of the other positions of the peptides.

Please cancel claim 31.

REMARKS

1. General Matters

1.1. On January 4, 2001, we filed a request to vacate. If the Examiner does not mail a new or supplemental action before the filing of this amendment, then this amendment is effectively a preliminary amendment, and the new or supplemental action must be responsive to it.

1.2. We have corrected the use of "I" in the specification.

1.3. As a result of this amendment, claims 22, 25, 26, 27, 30, 34 and 38 are amended, claim 31 is cancelled, and claims 25-30 and 32-38 now are pending.

2. Prior Art Issues

2.1. The claims were previously rejected for anticipation as follows

Reference	Claims	Amend

Pinilla	21-23	§2.1, 2.3
Huffman	21-23	§2.2
Spatola	23	§2.4
Cantley	21-22	§2.5
Holmes	21-23	§2.6

There were also obviousness rejections as follows:

Reference	Claims
Holmes	23
Pinilla + Huffman	21-22
Pinola + Spatola, Lebl or Holmes	23

The rejections still maintained are for anticipation and/or obviousness as follows:

Reference	Claims
Pinilla	25, 28-29, 31
Huffman	25, 28-29, 31
Spatola	32-38
Holmes	25, 28-29, 31

Claims 26 (display on cells), 27 (display on viruses), and 30 (R1 is tryptophan, proline or tyrosine) have not been rejected on prior art grounds. In view of this, claims 27 and 30 have been rewritten in independent form.

The rejection of claim 31 is moot as that claim has been cancelled.

2.2. Claims 32-38 have been rejected as obvious over

Spatola (1996).

2.2.1. Claim 32 is directed to a structured panel consisting of a plurality of biased combinatorial linear peptide libraries. In these libraries, there is a first fixed position which is fixed for all libraries in the panel, is the same residue for all peptides in a given library, and is more or less centrally located. There is also a second "scanning position" whose location is fixed for a given subpanel, but varies from subpanel to subpanel so as to scan the whole length of the peptide (other than the first position). This second position is the same amino acid for all peptides in a given library.

Spatola is distinguished in §2.4 of our last amendment:

> Claim 23 is rejected as anticipated by Spatola (1996) (OA §9). Spatola Table 1 presents a panel of 48 cyclic pentapeptide libraries. Residue 5 is Asp in all of the libraries. The Examiner points out that since the peptides are cyclic, the limitation "middle 50%" is meaningless. L1-L2 hold AA3 constant, L15-L24 hold AA2 constant, and so forth. Thus, there is one scanning residue, which scans positions 1-4, and corresponds to the "second position" of claim 23 (or 32). However, Spatola AA5 does not correspond to the "first position" of claim 23, since our base claim 21 requires that this AA "is not the same in all libraries of said panel".

The Examiner correctly points out that base claim 21 is cancelled. However, claim 32, like old 21, requires that "libraries of the panel collectively present a plurality of different residues at said first position". Spatola has only Asp at the nonscanning fixed position (5) and therefore does not anticipate claim 32. Nor does the Examiner explain why it would have been obvious to modify Spatola to make AA5 a position constant for any given library, but varying from library to

library within the panel.

In addition, claim 32 distinguishes Spatola because the claim is directed to a linear peptide library (in which the term "middle 50%" meaningfully limits which residue can be the nonscanning residue) while Spatola teaches only a cyclic peptide library. Indeed, Spatola teaches against linear peptide libraries because such peptides are not conformationally restrained.

The starting point for Spatola's synthesis was a single D-Asp linked to a solid phase support through its side chain β-carboxylic acid function. D-Asp was not added in any subsequent step. Hence, even though Spatola cyclized his peptides, he could identify the precyclization C-terminal of each peptide. Accordingly, it is still meaningful to speak of Spatola's peptides as having a middle 50%. The constant AA5 (the D-Asp) would have been outside this middle 50%.

New claim 32 is directed to a structured panel in which there are two, and only two, constant positions in any given library, where one position is fixed at the same location for all libraries (and is centrally located), and the other constant positions "scans" the remainder of the peptide.

Spatola describes a single library, rather than a structured panel of libraries. In Spatola's library, the D-Asp has a fixed position (AA5) for all libraries, but it is <u>not</u> in the middle 50%. There is also a scanning residue, but it scans only positions 3(L13-L24) and 4(L1-L12), not positions 1 and 2. Hence it does not "collectively scan all residue positions except for said first position".

2.2.2. Claim 35 is directed to the variant of page 29. This claim requires that the peptides be the result of DNA expression of mixed oligonucleotides with particular characteristics. Spatola did not provide peptides by expression.

The considerations mentioned in connection with claims 32 and 33 apply also to claim 35.

3. Definiteness Issues

A) Claims 32 and 33 are characterized as "omnibus"-type claims. Plainly they aren't; they recite numerous inclusions and exclusions. First, they are panels of linear peptide libraries, not of any other kind of molecule. Second, each library has exactly two constant residues, as opposed to libraries with no constant residues, one constant residue (e.g., the library of claim 31), or more than two constant residues. Third, there is a relationship between the position of the second constant residues in one library and the position of the second constant residue of another, as defined in the "subpanel" limitation. Fourth, the position of the absolute constant residue (the first one) is limited to a particular portion of the peptide.

B) The Examiner has questioned the terms "fixed", "screenable" and "structured panel".

The Examiner asserts that the term "fixed" is unclear in the absence of any peptide sequence. We do not understand why this would be the case. Claim 31 recites "each library having one and only one constant residue at a position fixed for all peptide in all libraries of said panel".

Consider a panel of the following libraries:

(1) Xaa Xaa Trp Xaa Xaa

(2) Xaa Xaa Pro Xaa Xaa

(3) Xaa Xaa Tyr Xaa Xaa.

Position 3 would be a fixed position satisfying the criterion of claim 31, as quoted above. That is, it is the position of the constant residue in each of libraries 1-3.

That is not the case if the panel were of these libraries:

(1') Xaa Trp Xaa Xaa Xaa

(2') Xaa Xaa Pro Xaa Xaa

(3') Xaa Xaa Xaa Tyr Xaa.

The aforementioned fixed position limitation would not be satisfied, as position 2 would be the constant residue position in library 1', position 3, in library 2', and position 4, in library 3'.

If one knows the amino acid reactants used at each step in the synthesis of a library, one may readily ascertain which steps added constant residues (by reaction with a pure AA) and which, variable ones (by reaction with an AA mixture). Moreover, even without such knowledge, one may surmise the identity of the constant and variable positions by sequencing a sampling of the peptides in the library. As few as 20 peptide sequences would provide a reasonably reliable identification assuming that only 20 amino acids were used at each position and that equal proportions were strived for.

If this analysis were repeated for each library in the panel of libraries, one could readily ascertain whether there is a particular residue position which (1) is constant within a given library and (2) variable from library to library.

The term "fixed" position or residue is used in several U.S. Patents, evidencing that it is not inherently confusing. See Olivera, USP 5,885,780; Spatola, USP 6,008,058; Cook, USP 5,587,471.

With regard to "screenable", this term has its plain meaning, that is "capable of being screened". We note in passing that the process limitation that the panel had been screened would not meaningfully limit the instant library claims as that screening would not further particularize the library structure.

We agree that "structured panel" is not an art-recognized term, but an inventor may serve as his own lexicographer. The term is formally defined at page 10, lines 1-8:

> A "structural panel" is a panel as defined above where there is some structural relationship between the member libraries. For example, one could have a panel of 20 different biased peptide libraries where, in each library, the middle residue is held constant as a given amino acid, but, in each library the constant residue is different, so, collectively, all 20 possible genetically encoded amino acids are explored by the panel.

We note that the term "structural panel" was used in that passage, but "structured panel" was clearly intended, see page 10, lines 16 and 22. We have corrected page 10, line 1 accordingly.

The definition noted above refers in turn to the definition of a panel at page 9, lines 33-38. This in turn refers to still earlier definitions on pages 8-9.

C) Claim 34 has been rewritten to overcome the antecedent basis problem.

D) Claim 35 is a product-by-process claim to a panel of peptide libraries. The nucleotides are recited in the process limitation. A product-by-process claim is not a duplicate of a product claim, see MPEP §2173.05(p)(I), even though for purpose of determining patentability over the prior art, only the structure of the product is considered, see MPEP §2113. It is not unusual for a single patent to include both a claim to a product, and a claim to the same product when made by a particular process. The process limitation is pertinent to infringement and hence avoids 112/4 problems. It can also be relevant to issues of enablement or description.

E) The terms "first" and "second" are arbitrary but not relative. It is customary in patent practice, when one needs to distinguish between two similar entities, to label one as the "first" such entity and the other as the "second". With regard

to explicit recitation of a "peptide sequence", see B above.

Description Issues (OA pp. 4-5)

These rejections apply only to claim 25-31.

A) The Examiner argues that the "middle 50%" teaching is directed just to the specific sequence of page 25, line 27. This is not true.

The sequence of page 25, line 27 is said at page 25, line 25 to be just "one embodiment" of the invention. This implies that other embodiments were contemplated.

At page 26, lines 2-7, Applicants teach

> Even if the chosen AA_1 is required (or at least permissive) of the TP binding activity, one may need particular flanking residues to assure that it is properly positioned. If AA_1 is more or less centrally located, the library presents numerous alternative choices for the flanking residues. If AA_1 is at an end, this flexibility is diminished.

We also direct the Examiner's attention to page 57, line 34 to page 58, line 8.

There is no reason to believe that these considerations would not apply to peptides longer than 41 a.a. (the longest peptide covered by the embodiment of page 25, lines 25-30). At page 121, lines 11-17, several proteins (Fas-R and TNF-R) are disclosed which are longer than 41 amino acids.

The formula at page 25 contemplates that AA_1 is the same amino acid for all peptides in the library, and that Xaa is any naturally occurring amino acid (or any except cysteine). Thus the formula of page 25, line 27 implies that there is only one constant residue. However, page 25 refers to the presence of one or more constant residues, and the possibility of two constant residues is further developed at pp. 28-30.

Moreover, one must distinguish between residues which are constant across all libraries of a panel (universally constant), and those which are constant within a given library but variable from library to library. If there is partial knowledge of an effective binding motif, one incorporates this knowledge into subsequent library designs by making the known motif residues universally constant. See page 18, lines 14-15; page 27, lines 12-14; page 57, lines 29-34; page 58, lines 2-3.

B) A "panel of combinatorial libraries" is defined at page 9, lines 33-38:

> A "panel of combinatorial libraries" is a collection of different (although possibly overlapping) and separately screenable simple or composite combinatorial libraries. A "panel" differ from a composite library in that the component simple libraries have not been mixed together, that is, they may still be screened separately.

Note that a "panel" is like a kit in that it comprises a plurality of components. There is no physical or chemical combination of the component libraries, hence no problem in "making" a panel. A "structured panel" is defined at page 10, lines 1-8, and in essence insists that a certain structural relationship exist between the member libraries. Hence it is a panel that lacks certain potential member libraries.

We also draw the Examiner's attention to "panel" patents, such as Johnson, USP 5,997,866, Foulkes, USP 5,665,543 (method claim1 6), Kauvar, USP 5,674,688 (claim 15), and Kauvar, 5,679,643 (claim 13).

Utility Issues (OA pp. 2-4)

Claims 25-38 have been rejected under 35 USC §101 for alleged lack of patentable utility.

Applicants have asserted that their structured panel of

combinatorial peptides is useful both directly in the identification of peptides which bind targets, and, indirectly, in the identification of small organic compounds which bind the same targets.

The Examiner has questioned whether this is a "substantial" utility, this is, a utility that has a "real world" use.

Here, the Examiner fails to distinguish between the utility of the panel as a whole, and the utility of an individual peptide included in that library. A claim to an individual peptide would not meet the utility requirement until a use for that specific peptide was known, e.g., that it bound a target of known biological activity. But we are claiming a structured panel of peptides that has been carefully designed so as to facilitate the identification of target-binding peptides and other target-binding molecules. The structured panel of libraries is a research tool.

The Examiner suggested that research tools are only those which are usable "to evaluate materials other than themselves".

However, we must be careful in interpreting what is meant by "other than themselves". An individual peptide is something other than a peptide library, especially if the peptide library is displayed on phage and the individual peptide is in free form. Thus, we would say that the claimed libraries are useful as "research tools" in evaluating the ability of individual peptides to bind to a particular target.

This is different from saying that the utility of a compound is in determining the properties of that very compound.

Moreover, the specification plainly discloses that the panels of peptides may be used to identify non-peptide compounds which bind a target. The basic procedure is set forth at page 17, line 33 to page 18, line 11. The ultimately useful compound is the one from the "complementary library", not the original

library. Thus, one could screen a peptide library to find peptides that bind the target, and then screen a benzodiazepine library (see page 39, line 11 to page 40, line 29) for benzodiazepines that inhibit the binding of the peptide (in labeled form) to the target. Plainly, a benzodiazepine is not a peptide. Thus, the peptide libraries are useful as research tools, in determining which benzodiazepines, carbamates, pyrrolidines, piperazines, etc. (see page 40, line 30 to page 44, line 11) might mediate the biological activity of the target.

As evidence that peptide libraries have a "real world" utility, we submitted evidence of the commercial availability of peptide libraries from New England Biolabs, Invitrogen, Novagen, Display System Biotech, and Stratagene.

In response, the Examiner said, in the paragraph bridging pp. 3-4 of the action,

> Applicants' arguments as to the pragmatic proof of the practical utility of combinatorial libraries is that such libraries are commercially bought and sold. Applicants rely upon the England Biolabs catalogue to show the commercial availability of a library kit. Applicants are not claiming a kit. Furthermore, all of these kits relate to a particular type of library unlike the instantly claimed undefined, unstructured etc. library. There is nothing of record that the alleged commerciality was not due to business events extraneous to the merits of the claimed invention. [See furhter Lebl et al (Biolopolymers (at e.g., page 177, Library techniques to page 178, col. 1.]

We would be happy to rephrase these "panel" claims as "kit" claims. As previously explained, a "panel" is really a kind of kit.

The NEB kit consists of a X_7, X_{10} or $C-X_7-C$ library (displayed on phage), gIII sequencing primer, a host E. coli

strain, control target and eluant, and detailed protocols. It is quite clear from the sales literature that the single most commercially important component of the kit is the library per se.

Moreover, there are libraries which have been sold by themselves, rather than as part of a kit, see, for example, Novagen's Pre-Made T7 Select™ Libraries (Exhibit A).

The Examiner asserts that the libraries which were sold were of a "particular type". If by this he means that they were "purpose-built", that is certainly not true. The Ph.D.-7 library is (Xaa)7, and the Ph.D.-12 library is (Xaa)12. Thus, unbiased libraries have been sold. It is true that the variable residues are fused to a carrier phase protein moiety, but the use of a different carrier moiety (which our claims do not require) would not alter the utility, as long as display was still achieved. Our structured panel, like the unbiased libraries that were sold, allows a full exploration of diversity for genetically encoded peptides of a given length.

We are perplexed by the Examiner's reference to "business events extraneous to the merits of the claimed invention". If we were touting the commercial success of the claimed invention as objective evidence of nonobviousness, it would be relevant to ask whether that success was attributable to the superiority of the invention, or to favorable pricing or unusual marketing efforts. Here, we are simply trying to show that peptide libraries as a class have real world utility. Whether they are priced high or low, one assumes that they would not be bought if they lacked real world utility.

The Brenner-Kirk-Joly trilogy held that if a chemical was not patentably "useful", then a process for making only that chemical, or starting materials and intermediates useable only in such a process, likewise are not patentable. Moreover, if a

chemical lacks a §101 utility, then a claim to a method of using that chemical would necessarily be unenabled under §112.

Nonetheless, the PTO has issued numerous patents to libraries per se, as well as to methods of making or using libraries[1] and this, too, is evidence that there is a consensus that libraries are patentably useful.

The following cases illustrate the relevance of prior patents:

> Ex parte Brian, 118 USPQ 242, 245, (POBA 1958) (past practice of office in accepting definiteness of "fingerprint" claims);
>
> In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979) (product claims reciting microorganisms previously treated as directed to statutory subject matter);
>
> Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ 2010, 2012 (Fed. Cir. 1988) (term "substantially" is "ubiquitous" in patent claims and therefore considered definite);
>
> In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999) (Construction of "restore hair growth" for purpose of determining both §112 enablement and §101 utility; prior art references may be indicative of how a claim term will be interpreted by those of ordinary skill in the art);
>
> Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d 1573, 1578-9 (Fed. Cir. 1996) (prior art used to demonstrate

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[1] As of February 5, 2001, there are 907 U.S. and foreign "molecular diversity" patents listed at http://www.5z.com/divinfo/patents.html, most being U.S. Patents. Counsel's non-exhaustive search on the USPTO database (as of February 20, 2001) revealed 677 patents with specified combinations of particular keywords in the claims (Ex. B).

how a disputed term is used by those skilled in the art, and indeed is more objective and reliable than post-litigation expert opinion testimony); Pioneer Hi-Bred International v. J.E.M. Ag Supply Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998) (issuance of Boehm USP 2,048,056 in 1936 is evidence that "in those instances where inventors showed they could define a reproducible plant meeting the limits of §112, plant patents were issued under §101".)

We have successfully screened our peptide libraries, and identified peptides which bind several targets. These include targets for which there is a commercial market for binding molecules:

Protein Kinase CβII - Panvera sells isoform-specific polyclonal antibodies for cell biology research, www.panvera.com.

human MDM2 - Santa Cruz Biotechnology sells polyclonal antibodies for research purposes, www.scbt.com (Ex. D); recent publication of a fungal metabolite, chlorofusin, that antagonizes binding of p53 to MDM2, Duncan et al., (2001) J. Am. Chem. Soc. 123:554-560. (enclosed Ex. C).

E coli ProRS - reagents available under the generic class of aminoacyl-tRNA synthetase enzymatic assay: tRNA, amino acids sold by Sigma, www.signma-aldrich.com (enclosed Ex. E).

H influenzae TyrRS - See above for aminoacyl-tRNA synthetase

beta-glucosidase - Sigma sells a variety of substrates and inhibitors (see enclosed Ex. F)

carboxypeptidase (B) -	Sigma sells substrate, hippuryl-Lys, and inhibitor protein (enclosed Ex. G)
alcohol dehydrogenase -	Sigma sells substrates β-NAD(H) and chemical inhibitors 4-Methylpyrazole Hydrochloride and Tetraethyylthiuram disulfide (enclosed Ex. H).
biotinylated ProRS -	see above for aminoacyl-tRNA synthetase
Estrogen Receptor -	Panvera sells Fluormone™ ES2, a fluorescein-labeled estrogen ligand, and polyclonal antibodies to Era & β isoforms; see enclosed for multiple applications (e.g., HTS, research) and details (Ex. I).

Attached hereto is a marked-up version of the changes made to the specification and claims by the current amendment. The attached page is captioned **"Version with markings to show changes made"**.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant

By: _____
Iver P. Cooper
Reg. No. 28,005

Enclosures
-Version with Markings to Show Changes Made
-Exhibits A-I

624 Ninth Street, N.W.
Washington, D.C. 20001
Telephone: (202) 628-5197
Facsimile: (202) 737-3528
IPC:lms
F:\,N\Nova\Fowlkes4B\PTOAMEND2.WPD

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In the specification

Paragraph beginning at line 1 of page 10 has been amended as follows:

--A "[structural] structured panel" is a panel as defined above where there is some structural relationship between the member libraries. For example, one could have a panel of 20 different biased peptide libraries where, in each library, the middle residue is held constant as a given amino acid, but, in each library the constant residue is different, so, collectively, all 20 possible genetically encoded amino acids are explored by the panel.--

Paragraph beginning at line 22 of page 25, has been amended as follows:

--A biased peptide library is one in which one or more (but not all) residues of the peptides are constant residues. The individual members are referred to as peptide ligands (PL). In one embodiment, an internal residue is constant, so that the peptide sequence may be written as

$$[(X_{aa})](Xaa)_m\text{-}AA_1\text{-}[(X_{aa})](Xaa)_n$$

Where Xaa is either any naturally occurring amino acid, or any amino acid except cysteine, m and n are chosen independently from the range of 2 to 20, the Xaa may be the same or different, and AA_1 is the same naturally occurring amino acid for all peptides in the library but may be any amino acid. Preferably, m and n are chosen independently from the range of 4 to 9.--

Paragraph beginning at line 26 of page 91, has been amended as follows:

--This example uses a eukaryotic cellular protein kinase as

a target for which we have isolated artificial ligands. The peptide sequences shown above could easily be used to set up a screen for small molecules which bind at the same site. The artificial ligand could be used in any of the ways discussed in example 1. We could also use any other cellular enzyme as a target. These selections may also be done in the presence of one or more cofactors or regulators of the enzymes function. In the case of PKC, we could have carried out the selection in the presence of diacyglycerol or phorbol esters to activate the enzyme. This would result in the enzyme taking on a different conformation and may alter the ligands that are obtained. This strategy may be altered to target a specific site by eluting the phage with the known ligand. To do this, [I] we would carry out all of the binding and amplification steps as above, however, the elution step would be replaced by an extended incubation in the presence of large amounts of the natural ligand (i.e. Phorbol). Alternatively, the pool of phage from the final round of selection could be "sorted" by adding the natural ligand first followed by the phage. The binding of the natural ligand would prevent the phage binding to a specific site but not at others. [I] We would then take the supernatant which contains the unbound phage and test individuals for binding. In this way you can enrich for phage to a specific known site. Sequence analysis of these phage would then yield a cluster of peptides which would describe the ligand binding site.--

Paragraph beginning at line 2 of page 103 has been amended as follows:

--Cellular receptors which span the membrane often need to be in a membrane to take on the correct conformation for a biologically active protein. This presents a problem for conventional techniques designed to find artificial ligands

targeted to the native form of the protein. One possible solution to this problem is the use of live cells to express the receptor of choice and then use the whole cell as the way to present the target to the library of artificial ligands. One system in which to do this is the oocyte from Xenopus laevis. [I] We would first clone the receptor of interest into a vector from which RNA could be produced *in vitro* using bacterial or phage RNA polymerases. This RNA would then be injected into oocytes and the oocytes then incubated to allow the production of protein. The oocytes (probably 1-10 per binding reaction), now with the receptor of interest on the cell surface would be mixed with the library of artificial ligands and binding allowed to occur. The oocytes would be washed to remove the non-specific binding ligands and then the ligands would be eluted using a change in pH, salt concentration or another treatment which would break the interaction. The ligands would then be amplified and subjected to further rounds of selection.--

In the claims:

Claims 22, 25, 26, 27, 30, 34, and 38 have been amended as follows:

22 (amended). The panel of claim [31] 27 wherein said peptides are of the form

$(Xaa)_m$-R1-$(Xaa)_n$,

where R1 is the amino acid at said first fixed position, and m and n do not differ by more than two.

25 (amended). The panel of claim [31] 30 in which the peptides are displayed on chromatographic supports.

26 (amended). The panel of claim [31] 27 in which the peptides are displayed on cells.

27 (amended). A structured panel consisting of a plurality of biased combinatorial linear peptide libraries, each library

having one and only one constant residue at a position fixed for all peptides in all libraries of said panel, wherein, in each library, said fixed position is (a) at least five residues from both ends of the peptides or (b) within the middle 50% of the peptides,

wherein the amino acid is assigned to said fixed position is not the same in all libraries of said panel,

each library being a separately screenable and physically distinct entity from all other libraries of the panel, [The panel of claim 31]

in which the peptides are displayed on viruses.

30 (amended). A structured panel consisting of a plurality of biased combinatorial linear peptide libraries, each library having one and only one constant residue at a position fixed for all peptides in all libraries of said panel, wherein, in each library, said fixed position is (a) at least five residues from both ends of the peptides or (b) within the middle 50% of the peptides,

wherein the amino acid is assigned to said fixed position is not the same in all libraries of said panel,

each library being a separately screenable and physically distinct entity from all other libraries of the panel in which the peptides are displayed on viruses

wherein said peptides are of the form

$(Xaa)_m$-R1-$(Xaa)_n$,

where R1 is the amino acid at said first fixed position, and m and n do not differ by more than two, [The panel of claim 22]

in which R1 is tryptophan, proline or tyrosine.

34 (amended). The panel of claim 33 where the panel has an overall diversity [of the panel] which is the same at each position of the peptides, and a given library has a [the] diversity [of the peptides in a given library] at a biased

position which does not exceed 3.

38 (amended). The panel of claim [31] 27 wherein the overall diversity of the panel at the fixed position of the peptides is the same as the overall diversity of the panel at each of the other positions of the peptides.

Claim 31 has been cancelled.